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Critical review

The involvement of the sigma-1 receptor in neurodegeneration and neurorestoration

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ABSTRACT

The sigma-1 receptor (Sig-1R) is a single 25 kD polypeptide and a chaperone protein immersed in lipid rafts of the endoplasmic reticulum (ER) where it interacts with mitochondria at the mitochondria-associated ER membrane domain (MAM). Upon activation, the Sig-1R binds to the inositol tri-sphosphate receptor (IP3R), and modulates cellular calcium (Ca^{2+}) homeostasis. Also, the activated Sig-1R modulates plasma membrane receptor and ion channel functions, and may regulate cellular excit-ability. Further, the Sig-1R promotes trafficking of lipids and proteins essential for neurotransmission, cell growth and motility. Activation of the Sig-1R provides neuroprotection and is neurorestorative in cellular and animal models of neurodegenerative diseases and brain ischaemia. Neuroprotection appears to be due to inhibition of cellular Ca^{2+} toxicity and/or inflammation, and neurorestoration may include balancing abberant neurotransmission or stimulation of synaptogenesis, thus remodelling brain con-nectivity. Single nucleotide polymorphisms and mutations of the SIGMAR1 gene worsen outcome in Alzheimer's disease and myotrophic lateral sclerosis supporting a role of Sig-1R in neurodegenerative disease. The combined neuroprotective and neurorestorative actions of the Sig-1R, provide a broad therapeutic time window of Sig-1R agonists. The Sig-1R is therefore a strong therapeutic target for the development of new treatments for neurodegenerative diseases and stroke.

1. Introduction

Neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) as well as acute brain injury, such as stroke or traumatic brain injury, are devastating conditions that lead to cell death and loss of critical brain functions (1–5). A major challenge for contemporary clinical neuroscience is to elucidate the mechanisms leading to cell death during these severe conditions and propose novel treatments that may alleviate or ameliorate subsequent brain dysfunctions. The loss of brain function is associated with neuronal degeneration in particular brain areas, but the activity of neurons in the vicinity of degenerated or degenerating cells, such as the peri-infarct tissue

after stroke, can also be depressed (3,6). Currently, new neuro-protective therapies are directed towards preventing degeneration of neurons at risk by abolishing the primary cause of cell death, such as aggregation of misfolded proteins seen in PD, AD or ALS, or by reinstating blood flow following stroke (thrombolysis). Another approach to limit tissue loss and decrease brain dysfunction is by protecting neurons against destructive processes caused by calcium (Ca^{2+}) and glutamate toxicity, oxidative stress or inflammatory processes (5). More recently, it has been demonstrated that it is possible to stimulate recovery or function of neurons not afflicted by disease or injury. This can be accomplished by attenuating dysfunction of neurotransmission, or by simulating brain plasticity thereby remodelling brain connectivity (6). As will be evident in this review, the Sig-1R has been implicated in many of these pro-cesses, reflecting its modulatory role in multiple cellular and physiological mechanisms (7,8). Hence, Sig-1R activation is clearly neuroprotective, but can also stimulate recovery of lost function by enhancing repair or plasticity mechanisms in intact healthy neu-rons of brains afflicted by disease or injury. In this overview we will therefore discuss the sigma-1 receptor (Sig-1R), (i) as a modulator

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of various cell destructive processes, (ii) as a stimulator of brain repair and plasticity, and (iii) as a factor affecting the risk for neurodegenerative diseases and stroke.

2. Neuroprotection by Sig-1R agonists

The Sig-1R is found throughout the body including brain cells: neurons, astrocytes, oligodendrocytes and microglia of the central nervous system (CNS) [9–15] it is bound to the ceramide-enriched microdomain, also called lipid rafts, in complex with the glucose-related protein 78/binding immunoglobulin protein (GRP78/BiP), an endoplasmic reticulum (ER) chaperone of the mitochondria-associated ER membrane (MAM) domain [16]. The polypeptide has two transmembrane sequences and the steroid binding domain-like I and II regions [17,18], which also bind cholesterol and other lipids [19] as well as synthetic Sig-1R ligands, such as neurosteroids, antipsychotics, antidepressants and psychostimulants [20]. Recently, dimethyl tryptamine has been identified as a potential endogenous ligand for the Sig-1R [21,22].

The neuroprotective actions of the Sig-1R have been reported using various agonists in experimental models of acute brain injury or neurodegeneration. In models of experimental stroke, agonists of the Sig-1R diminish infarct size and improve functional recovery. Using the Sig-1R agonist 4-phenyl-1-(4-phenylbutyl) piperidine (PPBP) administered intravenously starting 15 min prior to the end of ischaemia and then during reperfusion until the study endpoint at 4 h, showed a reduction of infarct volume in a cat model of transient middle cerebral artery occlusion (tMCAO) [23]. Importantly, the treatment did not affect cerebral blood flow during reperfusion. Similar results were obtained in rats subjected to 2 h of tMCAO and treated continuously with PPBP for 22 h starting 1 h after occlusion [24] or with (+) pentazocine [25]. Furthermore, a reduction of infarct size was also found in rats that were subjected to tMCAO and treated with PRE-084 (5 mg/kg i.p.) at 3 h into reperfusion with evaluation of infarct size at 2 days after permanent MCAO (pMCAO) [26]. Rats treated with the Sig-1R agonist dimemorfan starting 15 min before occlusion, and immediately or 2 h after tMCAO, display smaller infarcts than animals treated with vehicle. Importantly, the protective effect could be blocked by concurrent administration of the Sig-1R antagonist BD1047 [27]. Interestingly, acute administration of a low dose haloperidol, an antipsychotic drug and Sig-1R antagonist also displayed neuroprotection in ovariectomized rats 24 h after tMCAO [28]. Likewise, treatment prior to and at stroke onset with the selective serotonin reuptake inhibitor and Sig-1R agonist fluvoxamine resulted in smaller cortical infarcts and better neurological scores after pMCAO [29]. This neuroprotective effect was abolished by concomitant treatment with the antagonist NE-100. Together, these studies show that treatment with Sig-1R agonists during the acute phase after experimental stroke prevent brain tissue demise and enhance recovery of lost neurological functions. In other models of acute brain injury, PRE-084 treatment reduces lesion size in a model of excitotoxic perinatal brain injury [30]. Also, daily treatment with PRE-084 enhances survival of motoneurons after root avulsion injury [31].

Neuroprotection by Sig-1R agonists is also achieved in models of neurodegenerative disorders. Administration of PRE-084 for 35 days resulted in significant higher number of tyrosine hydroxylase (TH)-positive neurons in the lesioned dorsolateral striatum and pars compacta of the substantia nigra after a 6-hydroxydopamine (6-OHDA) lesion to the striatum associated with better functional outcome [11]. Likewise, in a model of ALS using the SOD1^{G93A} mice, the Sig-1R agonists PRE-084 [32,33] or SA4503 [34] attenuated the gradual loss of motoneurons.

The antidepressant actions of the Sig-1R agonists PRE-084 and (-)MR-22 in beta(25-35)-amyloid peptide-treated mice [35], prompted further neuroprotection studies using these compounds. In a cellular model of AD, beta(25-35)-amyloid peptide-induced neuronal death was significantly inhibited by concomitant treatment with PRE-084 or (-)MR-22. This protective effect could be abolished by co-application of the Sig-1R antagonist NE-100 [36]. The protective effect of (-)MR-22 was confirmed in an IgG saporin/ amyloid toxicity model [37]. Moreover, in the beta(25-35)-amyloid peptide model of AD, administration of the aminotetrahydrofuran derivate ANAVEX2-73, a mixed muscarinic and Sig-1R agonist, significantly blocked Tau phosphorylation, a hallmark of AD pathology [38]. Together, these studies show that Sig-1R activation may antagonize AD brain pathology, which was recently supported by a PET investigation showing a lower binding capacity for Sig-1R in patients with AD compared to age-matched individuals [39].

3. Mechanisms of neuroprotection by Sig-1R activation

3.1. Influence of Sig-1R on Ca^{2+} homeostasis

As a consequence of its cellular localization, distribution, and characteristics as a molecular chaperone, the Sig-1R can modulate multiple intracellular pathways and signalling cascades involving Ca^{2+} ions (Figs. 1 and 2). Since Ca^{2+} toxicity plays a pivotal role in cell death after stroke and neurodegenerative diseases, the Sig-1R-mediated effect on Ca^{2+} homeostasis may therefore be of crucial importance for its protective actions on the brain. At the MAM, Sig-1Rs are involved in the regulation of Ca^{2+} mobilization from ER stores. In addition, Sig-1Rs contribute to the stability of inositol trisphosphate receptor (IP3R) channels to ensure proper Ca^{2+} transport between the two organelles [9,17]. Furthermore, Sig-1Rs stimulate phospholipase C (PLC) resulting in increased levels of IP3 in the cytoplasm [40] with subsequent release of Ca^{2+} from the ER via activation of IP3R channels [41]. Furthermore, the acid sensing ion channel Ia [42,43], voltage sensitive Ca^{2+} channels [44], as well as AMPA and NMDA receptors [45], modulate intracellular Ca^{2+} levels and are regulated by Sig-1Rs. Neuroprotection by Sig-1R agonists could therefore be provided by preventing detrimental elevations of intracellular Ca^{2+}-mediated effects by these channels. Under these conditions, activated Sig-1Rs are involved in normalizing intracellular ischaemia- or acidosis-evoked Ca^{2+} overloads [46,47], an effect blocked by selective Sig-1R antagonists BD1047 and BD1063 [46].

3.2. Regulation of nNOS and apoptosis by Sig-1R

In neurons, recruitment and coupling of the Ca^{2+} dependent neuronal nitric oxide (NO) synthase (nNOS) to postsynaptic density protein 95 (PSD95) is inhibited by Sig-1R activation [48,49]. Subsequently, a reduction of nNOS in membrane fractions and nNOS association with the NR2 subunit of NMDA receptors has been described [49] resulting in a downregulation of the pro-apoptotic stress-regulated p38 mitogen-activated protein kinase (MAPK) [48].

Upon stress or injury, elevated cytoplasmic Ca^{2+} levels reduce nNOS phosphorylation increasing nNOS activity and leading to NO-induced protein kinase C (PKC)-dependent phosphorylation of NR1 [50]. Sig-1Rs also modulate the activity of pleiotropic transcription factors i.e. nuclear factor kappaB, cyclic adenosine monophosphate (cAMP) response element-binding protein and c-fos, which are involved in the regulation of immediate-early genes, cell metabolism and transport processes. These transcription factors can modulate pro- and anti-inflammatory genes as well as cell death and survival genes such as interleukins 8 and 10, *bcl-2* [51] and